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Tramadol with or without paracetamol (acetaminophen) for cancer pain (Review)

Wiffen PJ, Derry S, Moore RA

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[Intervention Review]

Tramadol with or without paracetamol (acetaminophen) for cancer pain

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ABSTRACT

Background

Tramadol is an opioid analgesic licensed for use in moderate to severe pain. It is considered as a low risk for abuse, so control regulations are not as stringent as for 'strong' opioids such as morphine. It has a potential role as a step 2 option of the World Health Organization (WHO) analgesic ladder.

Objectives

To assess the benefits and adverse effects of tramadol with or without paracetamol (acetaminophen) for cancer-related pain.

Search methods

We searched the following databases using a wide range of search terms: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and LILACS. We also searched three clinical trials registry databases. The date of the last search was 2 November 2016.

Selection criteria

We selected studies that were randomised, with placebo or active controls, or both, and included a minimum of 10 participants per treatment arm. We were interested particularly in blinded studies, but also included open studies.

We excluded non-randomised studies, studies of experimental pain, case reports, and clinical observations.

Data collection and analysis

Two review authors independently extracted data using a standard form and checked for agreement before entry into Review Manager 5. We included information about the number of participants treated and demographic details, type of cancer, drug and dosing regimen, study design (placebo or active control) and methods, study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events. We collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We assessed the evidence using GRADE and created a 'Summary of findings' table.

The main outcomes of interest for benefit were pain reduction of 30% or greater and 50% or greater from baseline, participants with pain no worse than mild, and participants feeling much improved or very much improved.

Main results

We included 10 studies (12 reports) with 958 adult participants. All the studies enrolled participants with chronic malignant tumour-related pain who were experiencing pain intensities described as moderate to severe, with most experiencing at least 4/10 with current treatment. The mean ages were 59 to 70 years, with participants aged between 24 and 87 years. Study length ranged from one day to six months. Five studies used a cross-over design. Tramadol doses ranged from 50 mg as single dose to 600 mg per day; doses of 300 mg per day to 400 mg per day were most common.

Nine studies were at high risk of bias for one to four criteria (only one high risk of bias for size). We judged all the results to be very low quality evidence because of widespread lack of blinding of outcome assessment, inadequately described sequence generation, allocation concealment, and small numbers of participants and events. Important outcomes were poorly reported. There were eight different active comparators and one comparison with placebo. There was little information available for any comparison and no firm conclusions could be drawn for any outcome.

Single comparisons of oral tramadol with codeine plus paracetamol, of dihydrocodeine, and of rectal versus oral tramadol provided no data for key outcomes. One study used tramadol combined with paracetamol; four participants received this intervention. One study compared tramadol with flupirtine - a drug that is no longer available. One study compared tramadol with placebo and a combination of cobrotoxin, tramadol, and ibuprofen, but the dosing schedule poorly explained.

Two studies (191 participants) compared tramadol with buprenorphine. One study (131 participants) reported a similar proportion of no or mild pain at 14 days.

Three studies (300 participants) compared tramadol with morphine. Only one study, combining tramadol, tramadol plus paracetamol, and paracetamol plus codeine as a single weak-opioid group reported results. Weak opioid produced reduction in pain of at least 30% from baseline in 55/117 (47%) participants, compared with 91/110 (82%) participants with morphine. Weak opioid produced reduction in pain of at least 50% in 49/117 (42%) participants, compared with 83/110 (75%) participants with morphine.

There was no useful information for any other outcome of benefit or harm.

Authors' conclusions

There is limited, very low quality, evidence from randomised controlled trials that tramadol produced pain relief in some adults with pain due to cancer and no evidence at all for children. There is very low quality evidence that it is not as effective as morphine. This review does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high. The place of tramadol in managing cancer pain and its role as step 2 of the WHO analgesic ladder is unclear.

PLAIN LANGUAGE SUMMARY

Tramadol with or without paracetamol (acetaminophen) for cancer pain

Bottom line

No firm conclusions could be drawn about the effectiveness or harms of tramadol, alone or with paracetamol, in cancer pain.

Background

One person in two or three who gets cancer will suffer from pain that becomes moderate or severe in intensity. The pain tends to get worse as the cancer progresses.

Tramadol hydrochloride is an opioid analgesic available since 1977. In 2016, tramadol, alone or in combination with paracetamol, was available in products for oral use and by injection from almost 90 companies. Oral formulations include those designed for immediate release, and for modified release over a longer time. Preparations for rectal administration are also available.

In this review, we set out to estimate how well tramadol worked, how many people had side effects, and how severe those side effects were - for example, whether they were so severe that participants stopped taking their tramadol.

Study characteristics

In November 2016, we found 10 studies with 958 adult participants and no studies in children. The studies were often small and compared different tramadol preparations with different comparator drugs, and did not report important outcomes well. This made it difficult to work out whether tramadol was as good or better or worse than any other drug for cancer pain.

Key findings

No firm conclusions could be drawn for any outcome in any comparison. Tramadol may not be as good as morphine.

Quality of evidence

We judged all the evidence available to be of very low quality. This means that the research does not provide a reliable indication of the likely effect.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Oral tramadol compared with oral morphine for cancer pain

Oral tramadol compared with oral morphine for cancer pain

Patient or population: people with pain due to cancer

Settings: any

Intervention: oral tramadol (any dose)

Comparison: oral morphine (any dose)

Outcomes	Probable outcome with tramadol	Probable outcome with morphine	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Participants with pain reduction of 30% or greater from baseline	55/117 (47%)	91/110 (82%)	Not calculated	227 (1 study)	Very low quality	1 study reporting on tramadol, tramadol + paracetamol and codeine + paracetamol.
Participants with pain reduction of 50% or greater from baseline	49/117 (42%)	83/110 (75%)	Not calculated	227 (1 study)	Very low quality	1 study reporting on tramadol, tramadol + paracetamol and codeine + paracetamol.
Participants with pain no worse than mild	No data		Not calculated	227 (1 study)	Very low quality	1 study reporting on tramadol, tramadol + paracetamol and codeine + paracetamol.
Participants with PGIC of much improved or very much improved	No data		Not calculated	227 (1 study)	Very low quality	1 study reporting on tramadol, tramadol + paracetamol and codeine + paracetamol.
Serious adverse events (death)	3/142	3/138	Not calculated	280 (2 studies)	Very low quality	1 of the 2 studies reported on tramadol, tramadol + paracetamol and codeine + paracetamol.
Other adverse events	No analysis possible		Not calculated		Very low quality	Inconsistent reporting between studies and comparators.
Withdrawals	No analysis possible		Not calculated		Very low quality	Inconsistent reporting between studies and comparators.

PGIC: Patient Global Impression of Change.

Descriptors for levels of evidence (EPOC 2015):
High quality: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate quality: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low quality: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low quality: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different: a large enough difference that it might affect a decision.

BACKGROUND

This review is one of a suite of reviews on the efficacy and safety of opioid medicines to treat cancer pain. These include reviews on buprenorphine (Schmidt-Hansen 2015a), fentanyl (Hadley 2013), hydromorphone (Bao 2016), oxycodone (Schmidt-Hansen 2015b), methadone (Nicholson 2017), morphine (Wiffen 2016), and tapentadol (Wiffen 2015).

Description of the condition

Cancer is estimated to cause over eight million deaths per annum - approximately 13% of deaths worldwide (IARC 2012). Globally, 32 million people are living with cancer. In the UK alone in 2014, there were around 350,000 new cases of cancer annually, with around 50% of people surviving for 10 years or more after diagnosis (Cancer Research UK 2016).

Cancer pain is perhaps one of the most feared symptoms associated with the disease. Pain may be the first symptom to cause someone to seek medical advice that leads to a diagnosis of cancer and 30% to 50% of all people with cancer will experience moderate to severe pain at some time (Portenoy 1999). Pain can occur at any time as the disease progresses but the frequency and intensity of pain tends to increase as the cancer advances (Portenoy 1999; van den Beuken-van Everdingen 2016). For people with advanced cancer, some 75% to 90% will experience pain having a major impact on daily living (Wiffen 2013). Pain had a significant negative correlation with quality of life (QoL) in studies of people with cancer in China, Japan, and Palestine, for example (Deng 2012; Dreidi 2016; Mikan 2016). Studies indicate that approximately 40% of patients suffered pain after curative treatment, 55% during cancer treatment and 66% in advanced disease and pain related to cancer is frequently described as distressing or intolerable by more than one third of patients (Breivik 2009; van den Beuken-van Everdingen 2016).

Cancer pain can be the result of the cancer itself, interventions to treat the cancer, and sometimes other underlying pains. Prevalence is also linked to cancer type, with head and neck cancer showing the highest prevalence. Age also has an impact with younger patients experiencing more pain (Prommer 2015). For this review, we will not consider postsurgical pain related to surgery or neuropathic pains due to chemotherapy.

The current World Health Organization (WHO) cancer pain ladder for adults recommends the use of weak opioids, with or without non-opioid analgesics, as the second step on the ladder (WHO 2016). The current National Institute for Health and Care Excellence in the UK advises that non-opioid analgesics alone be used for treating mild pain (0 to 3 on a 0 to 10 pain scale), together with a weak opioid for such as codeine or tramadol for mild to moderate pain (3 to 6), and with a strong opioid such as morphine for severe pain (6 to 10) (NICE 2016).

The effectiveness of the WHO cancer pain ladder has been examined from available evidence several times since the mid-1990s. These studies reported varying degrees of success, typically between 20% and 100% of people with cancer pain achieving good relief (Azevedo São Leão Ferreira 2006; Carlson 2016; Jadad 1995), with some suggesting that as many as 50% of people with cancer pain are under treated (Deandrea 2008). Some authorities have suggested that the second step on the ladder could be removed, and replaced with low doses of strong opioids such as morphine (Twycross 2014), which is currently the start of the third step.

Description of the intervention

Tramadol hydrochloride is an opioid analgesic originally marketed in West Germany in 1977. In 2016, tramadol, alone or in combination with paracetamol (acetaminophen), was available in products for oral use and by injection from almost 90 companies. Oral formulations include those designed for immediate release, and for modified release over a longer time. Preparations for rectal and parenteral administration are also available. The total oral daily dosage is usually up to 400 mg, although some licenses state that 400 mg is the maximum dose (Martindale 2016).

When combined with paracetamol, daily dosage is typically a maximum of eight tablets, each containing tramadol 37.5 mg and paracetamol 325 mg.

Tramadol is used to treat a range of different pain conditions. Tramadol differs from traditional opioids in not only acting as a μ-opioid agonist, but also having a range of other properties that may contribute to its analgesic effect, including serotonin reuptake inhibition and noradrenaline reuptake inhibition. It is licensed for use in moderate to severe pain and is less potent than morphine or similar drugs. It is considered to fit into step 2 of the WHO analgesic ladder (WHO 2016). In some parts of the world, tramadol is classified as a controlled substance (similar to codeine in this respect), but the exact classification and controls on prescribing vary markedly.

Tramadol has reasonable efficacy in acute postoperative pain as a single agent, and in combination with paracetamol (Edwards 2002; Moore 1997). It probably also has efficacy in neuropathic pain conditions (Hollingshead 2006), but has small benefits in osteoarthritis (Cepeda 2006). One previous systematic review concluded that the evidence base for tramadol was inadequate to recommend it as an alternative to paracetamol plus codeine for routine use in people with mild to moderate cancer pain (Tassinari 2011).

Tramadol is associated with typical opioid adverse events of nausea, dizziness, and dry mouth, although vomiting and constipation are thought to be less of a problem than with traditional opioids. Use of tramadol with concurrent serotonergic therapy poses a risk of serotonin syndrome (Beakley 2015).

Like other opioids, tramadol is subject to abuse. One study in Germany (looking at data from 1990 to 2009), where tramadol is not scheduled in the German Narcotic Drugs Act, calculated the incidence of abuse as 0.21 cases per million defined daily dosages (DDDs) and the incidence of dependency as 0.12 cases per million DDDs, with lower incidences in recent years (Radbruch 2013). The conclusion was that tramadol had a low potential for misuse, abuse, and dependency.

How the intervention might work

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine with a central analgesic effect. Both tramadol and its O-desmethyl metabolite are selective, weak OP3-receptor (μ) agonists. The mode of action is poorly understood (Minami 2015; Reeves 2008).

Tramadol is metabolised by N- and O-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulphation in the liver. Around 40% of the analgesic action of tramadol is provided by O-desmethyl tramadol (M1) created by rapid metabolism of tramadol in the liver via CYP2D6 (Bozkurt 2005; Grond 2004; Lintz 1998). Tramadol is also metabolised by N-demethylation via CYP3A4, and glucuronidation or sulphation in the liver (Grond 2004).

Tramadol is available as a racaemic mixture of (+) and (-) enantiomers. The (+) enantiomer has only a weak affinity to μ-opioid receptors and inhibits serotonin reuptake, while the (-) enantiomer inhibits noradrenaline reuptake in the spinal cord (Bozkurt 2005; Scott 2000). These different modes action might explain the longer analgesic efficacy and the lower incidence of opioid adverse effects, but a range of other modes of action have been proposed (Bozkurt 2005; Grond 2004).

Tramadol is rapidly absorbed after oral administration and has an absolute bioavailability of 65% to 70% (Lintz 1998; Scott 2000). Generally, there are no significant differences in the pharmacokinetics (elimination half-life, distribution, serum clearance, and concentration of metabolites) of tramadol between adults and children after oral dosing or intravenous injection. Genetic variances probably influence analgesic efficacy (Gan 2007). About 8% of the white population has CYP2D6 deficiency that reduces the analgesic effects of tramadol, and this may well be greater in some other populations (Pedersen 2005). Other drugs metabolised by CYP2D6 enzymes (e.g. ondansetron) can potentially interfere with tramadol metabolism, changing how well it works in individuals, and possible adverse events.

Why it is important to do this review

In many countries, strong opioids such as morphine are severely restricted, if available at all, and with wide variation in per capita use (see Pain & Policy Studies Group at University of Madison-Wisconsin; www.painpolicy.wisc.edu/opioid-consumption-data). This leaves many people with cancer at the risk of severe life-limiting pain. If tramadol, with or without paracetamol, is effective, it may provide an alternative for people with moderate to severe cancer pain. This review will inform policy makers such as the WHO on the possible utility of tramadol to treat cancer-related pain. It is hoped that the review will inform patients and carers on the value or otherwise of tramadol in this context.

A previous systematic review examined only oral tramadol, not the combination with paracetamol, included observational studies as well as randomised trials, and is now out of date (Tassinari 2011). Therefore, a new systematic review concentrating on randomised trial evidence is appropriate.

OBJECTIVES

To assess the benefits and adverse effects of tramadol with or without paracetamol (acetaminophen) for cancer-related pain.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they:

- were randomised (described as 'randomised' anywhere in the manuscript);
- ideally were double blind, but we also included open studies;
- had placebo or active controls, or both;
- included a minimum of 10 participants per treatment arm.

We excluded non-randomised studies, studies of experimental pain, case reports, and clinical observations. We included only studies that were fully published or available as extended abstracts (e.g. from clinical trials websites); we did not include short (usually conference) abstracts as these are often unreliable (PaPaS 2012).

Types of participants

Studies could include adults or children of any age who experienced cancer-related pain.

Types of interventions

Tramadol with or without paracetamol for cancer pain. Tramadol could be administered at any dose and by any route, and compared to placebo or any active comparator.

Types of outcome measures

Pain had to be measured using a validated assessment tool. For pain intensity, for example, this could be a 100-mm visual analogue scale (VAS) or 11-point numerical rating scale (no pain to worst pain imaginable) or a 4-point categorical scale (none, mild, moderate, severe), and for pain relief a 100-mm VAS (no relief to complete relief), or 5-point categorical scale (none, a little, some, a lot, complete or words to that effect). Measures of 30% or greater (moderate) and 50% or greater (substantial) reduction of pain over baseline are recommended outcomes for chronic pain studies from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin 2008). When considering Patient Global Impression of Change (PGIC), 30% or greater reduction of pain over baseline equates to much improved or very much improved, and 50% or greater reduction of pain over baseline equates to very much improved. We also used results equivalent to no pain or mild pain, because these are also outcomes acceptable to people with various types of pain (Moore 2013).

Primary outcomes

- Number of participants with pain reduction of 30% or greater from baseline.
- Number of participants with pain reduction of 50% or greater from baseline.
- Number of participants with pain no worse than mild (Moore 2013).
- Number of participants with PGIC of much improved or very much improved (or equivalent wording).

Secondary outcomes

- Quality of life (QoL).
- Use of rescue medication.
- Participant satisfaction or preference.
- Serious adverse events, including death.
- Other adverse events, particularly reports of effects of treatment on somnolence, appetite, or thirst (Wiffen 2014).
- Attrition: withdrawals due to lack of efficacy or adverse events.

Search methods for identification of studies

Electronic searches

We searched the following databases without language or date restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (via CRSO on 2 November 2016).
- MEDLINE (via Ovid, from 1947 to 2 November 2016).
- Embase (via Ovid, from 1974 to 2 November 2016).
- LILACS (via Birme, searched up to 2 November 2016).

We used a combination of Medical subject headings (MeSH), or equivalent, and text word terms and tailored search strategies to individual databases. The search strategies are in Appendix 1, Appendix 2, Appendix 3, and Appendix 4.

Searching other resources

We searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for unpublished (in journals) and ongoing trials. In addition, we checked the reference lists of reviews and retrieved articles for additional studies and performed citation searches on key articles. We planned to contact authors where necessary for additional information but we judged this to be unnecessary.

Data collection and analysis

Selection of studies

Two review authors (PW, SD) independently read the abstract of each study identified by the search, eliminated studies that clearly did not satisfy inclusion criteria, and obtained full copies of the remaining studies. Two review authors (PW, SD) independently read these studies to select relevant studies for inclusion, and, in the event of disagreement, a third review author (RAM) adjudicated. We did not anonymise the studies before assessment. We have included a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart to show the status of identified studies (Moher 2009) as recommended in Part 2, Section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We included studies in the review irrespective of whether they reported measured outcome data in a 'usable' way.

Data extraction and management

Two review authors (PW, SD) independently extracted data using a standard form and checked for agreement before entry into Review Manager 5 (RevMan 5) (RevMan 2014). We included information about the number of participants treated and demographic details, type of cancer, drug and dosing regimen, study design (placebo or active control) and methods, study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events. We collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We collected characteristics of the included studies in sufficient detail to complete a 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

Two review authors (PW, SD) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8, Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We completed a 'Risk of bias' table for each included study using the 'Risk of bias' tool in RevMan 5 (RevMan 2014).

We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved); high risk of bias (study was not blinded).
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study had a clear statement that outcome assessors were unaware of treatment allocation, and ideally described how this was achieved); unclear risk of bias (study stated that outcome assessors were blind to treatment allocation but lacked a clear statement on how it was achieved); high risk of bias (study was not blinded).
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); high risk of bias (used 'completer' analysis).
- Selective reporting (reporting bias). We assessed the risk of reporting bias as: low risk of bias (all intended outcomes reported); unclear risk of bias (any anomaly in reporting, such as participants contributing more than one set of data, or some outcomes not participant-reported); high risk of bias (prespecified outcome of interest not reported).

- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We planned to use dichotomous data to calculate risk ratios (RR) with 95% confidence intervals (CI) using a fixed-effect model, and calculate numbers needed to treat for one additional beneficial outcome (NNTs) as the reciprocal of the absolute risk reduction (McQuay 1998). In the event of significant statistical heterogeneity we would consider using a random-effects model. For unwanted effects, the NNT becomes the number needed to treat for one additional harmful outcome (NNH), and is calculated in the same manner.

We planned to use the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occurred with tramadol with or without paracetamol than with control (placebo or active) we used the term number needed to treat to prevent one event (NNTp).
- When significantly more adverse outcomes occurred with tramadol with or without paracetamol compared with control (placebo or active) we used the term number needed to harm or cause one event (NNH).

We did not plan to use continuous data for the primary outcomes because it is inappropriate where there is an underlying skewed distribution, as is usually the case with analgesic response.

Unit of analysis issues

The unit of randomisation was the individual participant.

Dealing with missing data

We planned to use intention-to-treat (ITT) analysis: participants who were randomised, took the study medication, and gave a minimum of one post baseline assessment.

We did not use imputation methods for any missing data.

Assessment of heterogeneity

We planned to assess statistical heterogeneity using L'Abbé plots, a visual method for assessing differences in results of individual studies (L'Abbé 1987), and by use of the I^2 statistic. We anticipated that there could be an effect of differences between participant characteristics, environment (inpatient versus outpatient), and outcome measures. We planned to explore these with subgroup and sensitivity analyses where there were sufficient data.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2010; Moore 2013). The review did not depend on what authors of the original studies chose to report or not.

We planned to undertake an assessment of publication bias if there were sufficient data for meta-analysis, using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNT of 10 or higher) (Moore 2008).

Data synthesis

We planned to undertake a quantitative synthesis if there were sufficient data, and present the data in forest plots. We planned to analyse studies of tramadol alone separately from the tramadol plus paracetamol combination. In the event of substantial heterogeneity, we would not show the totals in the forest plots.

- We planned to undertake a meta-analysis only if we judged participants, interventions, comparisons and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful.
- We planned to use RevMan 5 for meta-analysis (RevMan 2014), and Excel for NNTs and NNHs.

Quality of the evidence

We used the GRADE system to assess the quality of the evidence related to the key outcomes listed in Types of outcome measures, as appropriate (Appendix 5). Two review authors (PW, RAM) independently rated the quality of each outcome. We paid particular attention to inconsistency, where point estimates vary widely across studies or confidence intervals of studies show minimal or no overlap (Guyatt 2011), and potential for publication bias, based on the amount of unpublished data required to make the result clinically irrelevant (Moore 2008).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted, as recommended by GRADE guidelines (Guyatt 2013a). For example, if there were so few data that the results were highly susceptible to the random play of chance, or if a study used LOCF imputation in circumstances where there were substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the quality of the evidence by three levels, to very low quality. In circumstances where there were no data reported for an outcome, we have reported the level of evidence as very low quality (Guyatt 2013b).

There are also issues over both random chance effects with small amounts of data, and potential bias in small studies, especially in pain (Dechartres 2013; Dechartres 2014; Fanelli 2017; Moore 1998; Nguyen 2017; Nüesch 2010; Thorlund 2011). Cochrane Reviews have been criticised for perhaps over-emphasising results of underpowered studies or analyses (AlBalawi 2013; Turner 2013). However, it may be unethical to ignore potentially important information from small studies or to randomise more participants if a meta-analysis including small, existing studies provided conclusive evidence.

'Summary of findings' table

We included a 'Summary of findings' table as set out in the Pain, Palliative and Supportive Care Review Group author guide (PaPaS 2012), and recommended in Section 4.6.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The table includes, where possible, the number of participants with pain reduction of 30% or 50% or greater, participants with pain no worse than mild, and PGIC of much improved or very much improved. We have also included serious adverse events, other

adverse events, and withdrawals due to lack of efficacy or adverse events.

For the 'Summary of findings' table, we used the following descriptors for levels of evidence (EPOC 2015):

- **High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
- **Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
- **Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
- **Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different: a large enough difference that it might affect a decision.

Subgroup analysis and investigation of heterogeneity

We planned to analyse separately the data for tramadol alone and tramadol plus paracetamol, and to carry out sensitivity analyses for duration of study, age of participants (younger than 18 years versus 18 years or older). This was not possible because there were insufficient data.

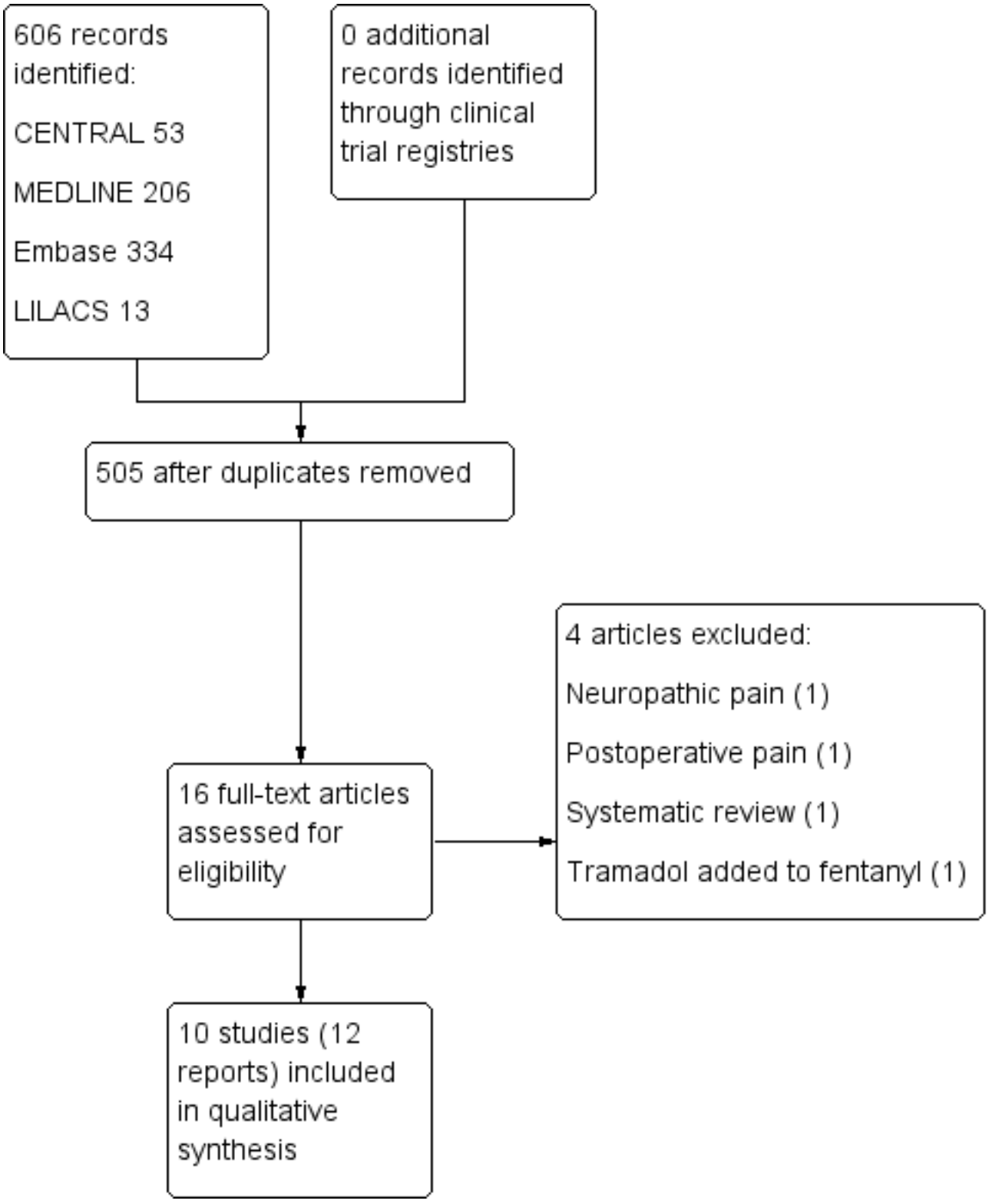
RESULTS

Description of studies

Results of the search

Searches in November 2016 identified 606 potentially relevant records in CENTRAL, MEDLINE, Embase, and LILACS. We identified no additional studies as extended abstracts in clinical trial registries, neither with nor without results. After screening titles and abstracts, we obtained the full text of 16 articles (Figure 1). A restricted search in May 2017 found no additional studies.

Figure 1. Study flow diagram.



Included studies

We included 10 studies (12 reports) with 958 adult participants (Bandieri 2016; Bono 1997; Brema 1996; Leppert 2001; Leppert 2010; Luben 1994; Mercadante 2005; Rodriguez 2007; Wilder-Smith 1994; Xu 2006). All the studies enrolled participants with chronic malignant tumour-related pain who were experiencing pain intensities described as moderate to severe, with most experiencing at least 4/10 with current treatment. The mean ages were 59 to 70 years, with participants aged between 24 and 87 years.

There were no studies in children. Study length ranged from one day (Xu 2006) to six months (Brema 1996).

Titration phase

Five studies titrated drugs to an effective dose (Bandieri 2016; Leppert 2001; Leppert 2010; Rodriguez 2007; Wilder-Smith 1994). One study adjusted doses within the treatment phases (Brema 1996). Mercadante 2005 used a basal dose but allowed additional drug for rescue.

Cross-over

Five studies used a cross-over design (Bono 1997; Leppert 2010; Mercadante 2005; Wilder-Smith 1994; Xu 2006). There was no standard approach. Mercadante 2005 followed a three-day regimen for each group, with no mention of washout between; Wilder-Smith 1994 used two four-day sessions with no washout; and Bono 1997 used one-week treatment periods, with a one-day washout between treatments. Leppert 2010 also used one-week treatment periods, but with no washout. Xu 2006 used single dose cross-overs, and the timing was not well explained.

Doses of tramadol

Doses ranged widely from 50 mg as single dose (Xu 2006) to 600 mg per day (Leppert 2001; Leppert 2010). Doses of 300 mg per day to 400 mg per day were most common.

Only one study used tramadol combined with paracetamol, and only four participants received this intervention (Bandieri 2016).

Comparators

One of the studies compared tramadol to placebo (Xu 2006).

Active comparators were:

- oral morphine (Bandieri 2016; Leppert 2001; Wilder-Smith 1994);
- buprenorphine (Bono 1997; Brema 1996);
- dihydrocodeine (DHC) (Leppert 2010);
- flupirtine (Luben 1994);
- hydrocodeine (Rodriguez 2007);
- paracetamol plus codeine (Rodriguez 2007);
- cobrotoxin plus tramadol plus ibuprofen (Xu 2006);
- rectal formulation of tramadol (Mercadante 2005).

Excluded studies

We excluded four potentially relevant studies after reading the full text (Arbaiza 2007; Marinangeli 2007; Tassinari 2011; Yavuz 2004). The reasons were that they studied neuropathic pain (Arbaiza 2007) or postoperative pain (Yavuz 2004), used tramadol plus fentanyl (Marinangeli 2007), or were a systematic review (Tassinari 2011).

Risk of bias in included studies

Risks of bias are shown in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

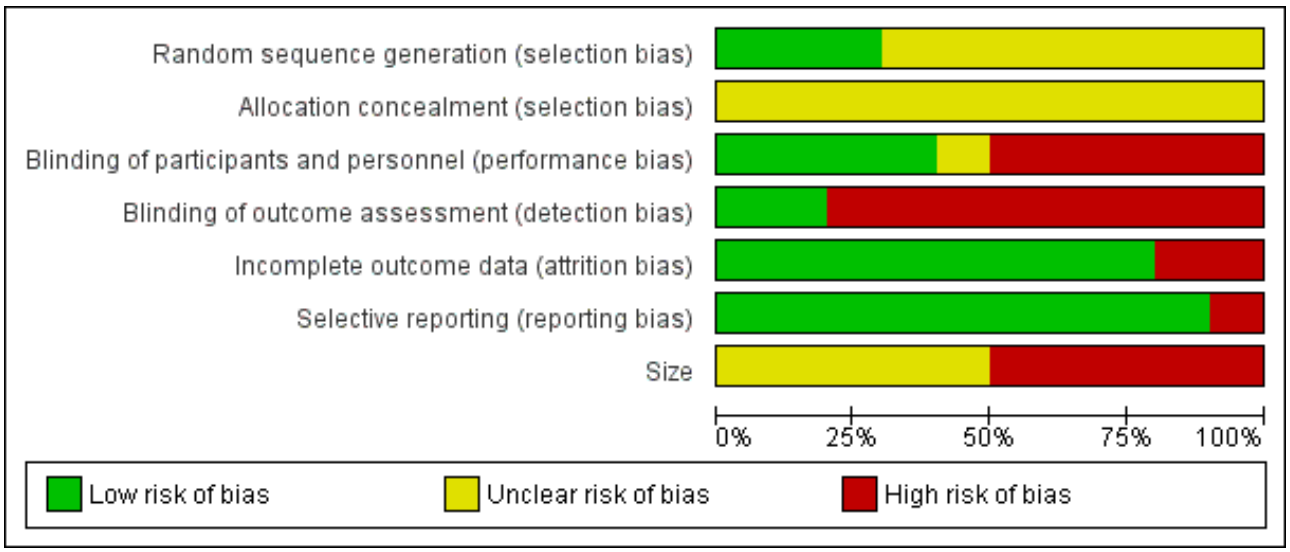
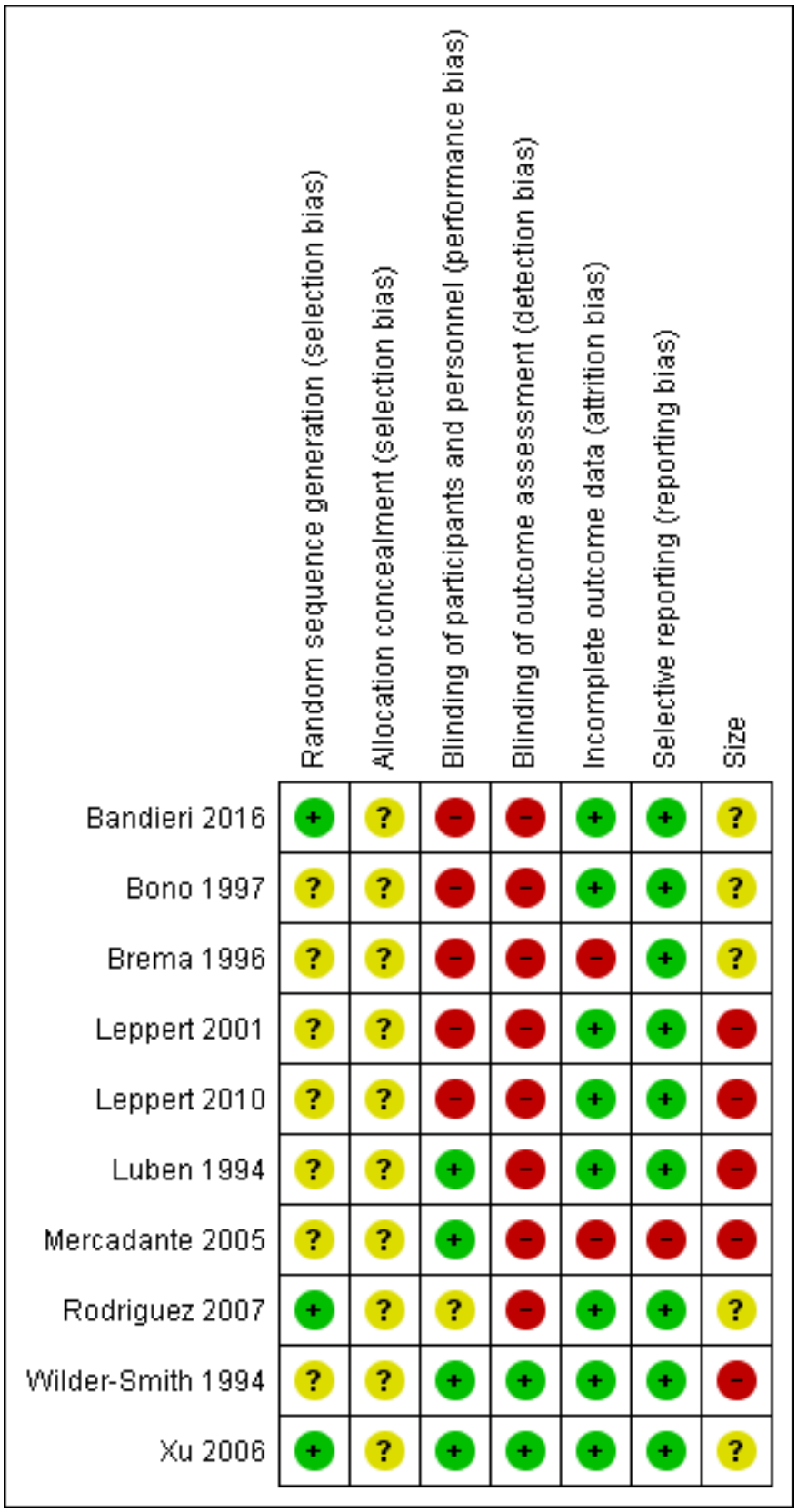


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All the studies stated that they were randomised, but only three reported adequate methods of sequence generation (Bandieri 2016; Rodriguez 2007; Xu 2006). No study described how allocation concealment was managed.

Blinding

Four studies adequately reported the methods used to maintain blinding of participants and study personnel (Luben 1994; Mercadante 2005; Wilder-Smith 1994; Xu 2006). Rodriguez 2007 reported that "drugs were packaged in identical containers" which we judged to be unclear. The remaining five studies were not blind and so were at high risk of bias.

Only two studies were judged at low risk of detection bias (Wilder-Smith 1994; Xu 2006); others were judged at high risk.

Incomplete outcome data

Two studies were judged at high risk for incomplete outcome reporting (Brema 1996; Mercadante 2005). There were no other problems identified.

Selective reporting

One study was judged at high risk for selective outcome reporting (Mercadante 2005). There were no other problems identified.

Other potential sources of bias

None of the included studies enrolled 200 or more participants per treatment arm, which we consider is the minimum required to give confidence in the results. Five studies enrolled fewer than 50 participants per treatment arm (Leppert 2001; Leppert 2010; Luben 1994; Mercadante 2005; Wilder-Smith 1994), which brings the validity of these studies into question. Three of the five studies had a cross-over design (Leppert 2010; Mercadante 2005; Wilder-Smith 1994).

Effects of interventions

See: **Summary of findings for the main comparison** Oral tramadol compared with oral morphine for cancer pain

Because of the small amount of information available for tramadol, alone or combined with paracetamol, for any outcome, and in any comparison, we judged the evidence to be very low quality throughout. In addition to small size, other issues influencing our judgement were widespread lack of blinding of outcome assessment, unclear methods of sequence generation and allocation concealment, and poor reporting of important outcomes. We have summarised the main results in Summary of findings for the main comparison.

Pain

Tramadol versus morphine

Three studies (300 participants) compared tramadol with morphine (Bandieri 2016; Leppert 2001; Wilder-Smith 1994). Bandieri 2016 regarded tramadol, tramadol plus paracetamol, and paracetamol plus codeine as a single weak opioid group. Of the 122 participants who received weak opioids, 23 received either tramadol alone (19 participants) or tramadol plus paracetamol (4four participants). Therefore, results in this study need to be treated with caution and are not a reliable indication of the effects of tramadol.

Number of participants with pain reduction of 30% or greater from baseline

In the weak opioid group as a whole, 55/117 (47%) participants achieved a reduction in pain of at least 30% from baseline, compared with 91/110 (82%) participants in the morphine group (Bandieri 2016).

Leppert 2001 and Wilder-Smith 1994 did not report number of participants with pain reduction of 30% or greater from baseline.

Number of participants with pain reduction of 50% or greater from baseline

In the weak opioid group as a whole, 49/117 (42%) participants achieved a reduction in pain of at least 50% from baseline, compared with 83/110 (75%) participants in the morphine group (Bandieri 2016).

Leppert 2001 and Wilder-Smith 1994 did not report number of participants with pain reduction of 50% or greater from baseline.

Number of participants with pain no worse than mild

We were unable to determine the number of participants with pain no worse than mild from any of the studies.

Number of participants with PGIC of much improved or very much improved (or equivalent wording)

We were unable to determine number of participants with PGIC of much improved or very much improved from any of the studies.

Quality of life

Only Leppert 2001 reported QoL outcomes. On the 35th day, emotional functioning was significantly better in the morphine group but participants in this group had more financial problems. There were no significant differences in other functioning.

Use of rescue medication

Bandieri 2016 reported that 41/117 participants in the weak opioid group and 17/110 in the morphine group were switched to another strong opioid; 33/117 required an increase in dose in the weak opioid group compared with 15/110 in the morphine group.

Wilder-Smith 1994 reported that 8/20 participants in the tramadol group requested additional medication, compared with 7/20 in the morphine group.

Leppert 2001 did not report use of rescue medication.

Participant satisfaction or preference

Wilder-Smith 1994 reported that 3/20 participants preferred tramadol, 8/20 preferred morphine, and 9/20 expressed no preference.

Leppert 2001 reported that 16/20 participants in both the tramadol and morphine groups preferred the sustained release versions. As this was a parallel group study, it was not possible for participants to express a preference between tramadol and morphine.

Bandieri 2016 did not report participant satisfaction or preference.

Tramadol versus buprenorphine

Two studies (191 participants) compared tramadol with buprenorphine (Bono 1997; Brema 1996).

Number of participants with pain reduction of 30% or greater from baseline

We were unable to determine number of participants with pain reduction of 30% or greater from baseline from either of the studies.

Number of participants with pain reduction of 50% or greater from baseline

We were unable to determine number of participants with pain reduction of 50% or greater from baseline from either of the studies.

Number of participants with pain no worse than mild

At 14 days, 60/68 (88%) participants receiving tramadol and 47/63 (75%) participants receiving buprenorphine reported having no worse than mild pain (data derived from graph) (Brema 1996). Bono 1997 did not report number of participants with pain no worse than mild.

Number of participants with PGIC of much improved or very much improved (or equivalent wording)

We were unable to determine number of participants with PGIC of much improved or very much improved from either of the studies.

Quality of life

Bono 1997 reported the use of the Karnofsky performance indicator for QoL; there was little change in the index over the course of the study. Brema 1996 did not report on QoL.

Use of rescue medication

We were unable to determine use of rescue medication from either of the studies.

Participant satisfaction or preference

More participants favoured tramadol in the Bono 1997 study, but this was based on reports from both participants and investigators. Brema 1996 did not report participant preference.

Tramadol versus dihydrocodeine (DHC)

One study (40 participants) compared tramadol with dihydrocodeine (Leppert 2010).

Number of participants with pain reduction of 30% or greater from baseline

We were unable to determine number of participants with pain reduction of 30% or greater from baseline from this study.

Number of participants with pain reduction of 50% or greater from baseline

We were unable to determine number of participants with pain reduction of 50% or greater from baseline from this study.

Number of participants with pain no worse than mild

We were unable to determine number of participants with pain no worse than mild from this study.

Number of participants with PGIC of much improved or very much improved (or equivalent wording)

We were unable to determine number of participants with PGIC of much improved or very much improved from this study.

Quality of life

Participants reported better scores of emotional functioning in the tramadol group, and better global QoL scores and better cognitive functioning in the DHC group.

Use of rescue medication

Twelve participants in the tramadol group and eight in the DHC group required rescue medication.

Participant satisfaction or preference

Four participants preferred tramadol and 19 preferred DHC.

Tramadol versus paracetamol plus codeine

One study (177 participants), published in two reports, compared tramadol with paracetamol plus codeine (Rodriguez 2007).

Number of participants with pain reduction of 30% or greater from baseline

We were unable to determine number of participants with pain reduction of 30% or greater from baseline from this study.

Number of participants with pain reduction of 50% or greater from baseline

We were unable to determine number of participants with pain reduction of 50% or greater from baseline from this study.

Number of participants with pain no worse than mild

We were unable to determine number of participants with pain no worse than mild from this study.

Number of participants with PGIC of much improved or very much improved (or equivalent wording)

We were unable to determine number of participants with PGIC of much improved or very much improved from this study.

Quality of life

We were unable to determine QoL from this study.

Use of rescue medication

We were unable to determine use of rescue medication from this study.

Participant satisfaction or preference

We were unable to determine participant satisfaction or preference from this study.

Oral tramadol versus rectal tramadol

One study (60 participants) compared oral tramadol with rectal tramadol (Mercadante 2005).

Number of participants with pain reduction of 30% or greater from baseline

We were unable to determine number of participants with pain reduction of 30% or greater from baseline from this study.

Number of participants with pain reduction of 50% or greater from baseline

We were unable to determine number of participants with pain reduction of 30% or greater from baseline from this study.

Number of participants with pain no worse than mild

We were unable to determine number of participants with pain no worse than mild from this study.

Number of participants with PGIC of much improved or very much improved (or equivalent wording)

We were unable to determine number of participants with PGIC of much improved or very much improved from this study.

Quality of life

We were unable to determine QoL from this study.

Use of rescue medication

There were no differences between oral and rectal tramadol in the number of rescue doses used.

Participant satisfaction or preference

The study reported that participants preferred the oral route, but no data were provided.

Tramadol versus flupirtine

One study (71 participants) compared tramadol with flupirtine (Luben 1994). The use of flupirtine, a non-opioid analgesic, is now severely restricted due to liver toxicity (EMA 2013). The only relevant outcome reported in this study was the use of rescue medication by 31/36 in the tramadol group and 23/35 in the flupirtine group.

Tramadol versus cobrotoxin

One study (119 participants) compared tramadol with cobrotoxin plus tramadol plus ibuprofen (Xu 2006). This study had two parallel treatment arms in which participants took single doses of the cobrotoxin combination, placebo, and tramadol. One arm took the cobrotoxin combination first and the tramadol last, while the other took the tramadol first and the cobrotoxin combination last. If participants failed to get adequate pain relief from the first dose within one hour, they were instructed to take the next dose in the sequence (and presumably the third dose if no benefit). A period of one hour seems very short for tramadol to reach full effect, and an additional hour following placebo would not provide an adequate washout. For these reasons, we decided that it was impossible to use the results.

Serious adverse events (including death)

There was inconsistent reporting of serious adverse events across all comparisons.

Bandieri 2016 reported death in 1/122participants receiving weak opioid (not stated which opioid) and 2/118 receiving morphine. Leppert 2001 reported death in 2/20 in the tramadol group and 1/20 in the morphine group.

Brema 1996 reported withdrawal from the study due to disease progression or death in 27/68 participants with tramadol group, and 22/63 with buprenorphine, but there was no indication of whether this was judged related to the interventions.

Leppert 2010 reported that there were no serious adverse events or deaths, and Luben 1994 reported that one participant withdrew with itchy erythema from flupirtine treatment, but it is unclear whether this was judged a serious adverse event. The remaining studies did not report on serious adverse events or deaths.

Other adverse events, particularly reports of effects of treatment on somnolence, appetite, or thirst

There was inconsistent reporting of other adverse events across all comparisons.

Only four studies provided data for participants experiencing any adverse event with tramadol (Brema 1996; Leppert 2001; Wilder-Smith 1994; Xu 2006). In total 29 participants out of 267 experienced an adverse event (11%).

Four studies provided data on somnolence (Bono 1997; Brema 1996; Luben 1994; Rodriguez 2007). Somnolence was reported by 42 participants in a population of 220 (19%). Effects on appetite and thirst were only reported in one study (Rodriguez 2007); 12/56 reported appetite related issues and 12/56 reported a dry mouth.

Attrition

Withdrawals due to lack of efficacy

Six studies provided data on withdrawals due to lack of efficacy (Bono 1997; Brema 1996; Leppert 2001; Leppert 2010; Wilder-Smith 1994; Xu 2006). In total, 31/327 (9.5%) participants withdrew due to lack of efficacy.

Withdrawals due to adverse events

Most studies reported withdrawals due to adverse events or poor tolerability; they were not reported in Rodriguez 2007, and were reported in a separate publication for Leppert 2010, in Polish. In the remaining studies, the rate of withdrawals varied greatly between studies, but there was no obvious difference between tramadol and any of the comparators used, except possibly for buprenorphine in one study (Bono 1997), but not the other (Brema 1996).

DISCUSSION

Summary of main results

No firm conclusions could be drawn for any outcome in any comparison.

There is very limited very low quality evidence that tramadol is not as effective an analgesic for cancer pain as morphine, but this is not surprising. We were able to determine the proportion of participants who achieved an outcome of 'no worse than mild pain' in only one study (Brema 1996; 60/68 participants with tramadol). In two studies, tramadol was similar to buprenorphine at the doses used. Comparisons with dihydrocodeine and codeine did not provide any useful data. In one small study, rectal tramadol was equivalent to oral tramadol. Comparisons with flupirtine are not relevant as flupirtine is no longer available. There was no useful information about tramadol combined with paracetamol.

Overall completeness and applicability of evidence

Given the widespread use of tramadol in palliative care, the amount of underpinning data is small. The most recent study compared tramadol with morphine (Bandieri 2016). Tramadol has a potential

role on step 2 of the analgesic ladder, but good quality studies comparing tramadol with other step 2 drugs (e.g. codeine or dihydrocodeine) are missing, and there are no good data on those drugs either. Some authors have suggested eliminating the second step of the analgesic ladder, with weak opioids being replaced with low doses of oral morphine (Twycross 2014).

There were insufficient data to carry out any subgroup analyses. In particular, we were unable to investigate the influence of dose and titration regimen on either efficacy or tolerability. Included studies were underpowered to investigate serious adverse events.

We identified no studies in children.

Quality of the evidence

The evidence base identified by this review was small and limited in scope due to the small number of participants included in the different comparisons and the diversity of the study methodologies and outcome reporting. While not blinding treatments might be expected in older studies, two of the more recent studies were at high risk of bias due to a lack of blinding (Bandieri 2016; Leppert 2010).

Because of the small amount of information available for tramadol, alone or combined with paracetamol, for any outcome, and in any comparison, we judged the evidence to be very low quality throughout. Cochrane Reviews have been criticised for over-emphasising results of underpowered studies or analyses (AlBalawi 2013; Turner 2013); small numbers of participants and events for important comparisons was a major issue in this review. As well as small size, other issues influencing our judgement were widespread lack of blinding of outcome assessment, unclear methods of sequence generation and allocation concealment, and poor reporting of important outcomes.

Potential biases in the review process

We are unaware of any potential biases in the review process.

Agreements and disagreements with other studies or reviews

We identified one published systematic review (Tassinari 2011). The authors stated, "Data supporting ...oral tramadol as an alternative to codeine plus paracetamol are insufficient to recommend its routine use in cancer patients with mild to moderate cancer pain." Our review, with 10 randomised studies, has more studies that the previous review, which also included abstracts, non-randomised studies, and different types of cancer pain, including neuropathic pain.

A number of other reviews have examined both the weak opioid codeine (Straube 2014), and strong opioids buprenorphine (Schmidt-Hansen 2015a), morphine (Wiffen 2016), oxycodone (Schmidt-Hansen 2015b), and tapentadol (Wiffen 2015). The amount of evidence in some of these reviews was also limited. For example, the review of codeine, with or without paracetamol, included 15 studies and 751 participants, but was unable to provide any good information on efficacy or adverse events (Straube 2014). The review on oral morphine had the largest amount of useable data, reporting that in 17 studies, 'no worse than mild pain' was achieved by 362/377 (96%) participants, and an outcome equivalent to treatment success in 400/638 (63%) participants (Wiffen 2016).

AUTHORS' CONCLUSIONS

Implications for practice

For people with cancer pain

There is limited very low quality evidence from randomised controlled trials that tramadol produces pain relief in some adults with pain due to cancer. The place of tramadol in managing cancer pain is unclear.

For clinicians managing cancer pain

There are few options to treat mild to moderate cancer pain before moving to strong opioids such as morphine. There is no clear evidence to support the use of tramadol in mild to moderate pain, or severe pain.

For policy makers

Tramadol may have a role if other opioids are not tolerated, providing the issues of dose titration and possible severe adverse effects are considered. There is no information for the use of tramadol in paediatrics.

For organisations or bodies making decisions about funding treatment options

Tramadol may have a place on formularies but its role as an analgesic for cancer pain is unclear.

Implications for research

General implications

Research in this patient population is challenging, and a large trial of high quality that minimises bias has not been conducted. Furthermore, there are few options for step 2 on the WHO analgesic ladder.

Implications for study design

Key issues for study design are now well understood, yet we continue to see published studies that do not adequately describe randomisation and allocation concealment. Blinding of studies is still not routinely undertaken, and numbers of participants remain low (Bandieri 2016). These issues should be of concern to research ethics committees.

Implications for measurement and outcomes

As the distribution of response to analgesics is often bimodal, we strongly recommend the collection of dichotomous data in preference to mean pain scores. Data should be available to allow the estimation of the proportion of participants who achieve no worse than mild pain, defined as below 30 mm on a 100-mm visual analogue scale (VAS) pain intensity scale. Adverse events should always be reported but we advocate specific reporting of events affecting appetite, thirst, consciousness, and somnolence - issues that seriously affect people's lives in the last stages of illness.

Other considerations for future study design include:

- use of standard and comparable pain intensity scores, which would allow closer comparison between different studies and potentially facilitate meta-analysis;
- inclusion of only participant-reported pain and other data;
- larger numbers of participants in studies where differentiation by condition has been attempted, to answer the question as to whether tramadol is particularly valuable in cancer-related bone or neuropathic pain;
- participant satisfaction and quality of life appraisal.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bandieri 2016

Methods	Multicentre, randomised, open-label, parallel group. Duration: 28 days.

Bandieri 2016 *(Continued)*

Participants	240 participants. Moderate cancer pain (mostly visceral and somatic) scoring 4/10 to 6/10 on NRS, opioid naive. Median age 68 years. Male 56%.
Interventions	Weak opioid: tramadol alone up to 400 mg/day, or tramadol + paracetamol, or paracetamol 4000 mg + codeine up to 180 mg daily, n = 122 (tramadol alone = 19, tramadol + paracetamol = 4). Morphine up to 30 mg/day modified release following titration, n = 118.
Outcomes	Responders with > 20% reduction in PI. Responders with > 30% reduction in PI. Responders with > 50% reduction in PI. Use of rescue medication. Adverse events. Withdrawals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Centralized using a computer-generated procedure."
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems identified.
Selective reporting (reporting bias)	Low risk	No problems identified.
Size	Unclear risk	122 participants in weak opioid group, 118 participants in morphine group.

Bono 1997

Methods	Randomised, open-label, cross-over study. Duration 29 days: 1 week washout, 1 week 1st intervention, 1 day washout, 1 week 2nd intervention.
Participants	60 participants with advanced tumours, baseline PI 60/100. Mean age 61 years. Male 73%.

Bono 1997 *(Continued)*

Interventions	Tramadol oral 100 mg 3 times daily. Buprenorphine 0.2 mg 3 times daily.
Outcomes	PI: 100-mm VAS during first 3 hours of study and at end of each treatment period. QoL. Use of rescue medication. Participant satisfaction. Adverse events. Withdrawals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised, method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems identified.
Selective reporting (reporting bias)	Low risk	No problems identified.
Size	Unclear risk	60 participants in cross-over.

Brema 1996

Methods	Multicentre, randomised, open-label, parallel group. Duration: up to 6 months.
Participants	131 participants with strong to unbearable tumour pain no longer responsive to NSAIDs. Mean age 59 years (range 27 to 82). Male 66%.
Interventions	Tramadol 100 mg modified release every 8 to 12 hours up to 400 mg/day, n = 68.

Brema 1996 *(Continued)*

	Buprenorphine 0.2 mg sublingual every 6 to 8 hours, n = 63.
Outcomes	PI: 6-point NRS at baseline and days 7, 14 then monthly. Type of pain. PI: 100-mm VAS. PR: 6-point VRS. Patient acceptability. Adverse events. Withdrawals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomisation list"; method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Approximately one third of participants dropped out in each group. Imputation not mentioned.
Selective reporting (reporting bias)	Low risk	No problems identified.
Size	Unclear risk	131 participants.

Leppert 2001

Methods	Randomised, open-label, parallel group. Duration: 7-day titration, 28 days' stable dose.
Participants	40 participants with moderate to severe cancer pain (PI ≥ 45/100, mean at baseline 80/100), opioid naive. Mean age and sex not reported.
Interventions	Tramadol titrated up to 600 mg CR daily, n = 20. Morphine up to 200 mg CR daily, n = 20.

Leppert 2001 *(Continued)*

	Medication supplied as standard release formulations during titration to PI < 50/100 or ≤ moderate, then doses converted to modified release.
Outcomes	PI: VAS and 5-point VRS. PR: 5-point VRS. Participant preference. QoL: EORTC. Adverse events. Withdrawals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"List of random assignment prepared by Statistical Dept."
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems identified.
Selective reporting (reporting bias)	Low risk	No problems identified.
Size	High risk	40 participants in cross-over.

Leppert 2010

Methods	Single centre, randomised, open-label, cross-over study. Duration: 2 × 7-day treatment periods; no washout period.
Participants	40 participants with cancer pain of moderate intensity (≥ 40/100) with non-opioid therapy, opioid naive. Mean age 70 years. Male 37% of completers.
Interventions	Tramadol titrated up to maximum 600 mg CR daily. Dihydrocodeine titrated up to maximum 360 mg CR daily.

Leppert 2010 *(Continued)*

	Dose titrated to effect (PI < 40/100 or decrease by ≥ 20/100. Previous treatment with NSAIDs, paracetamol, metamizole allowed.
Outcomes	PI: 100-mm VAS. QoL: EORTC. Performance status. Participant preference. Use of rescue medication. Serious adverse events. Withdrawals.
Notes	Details about adverse events reported in a separate paper, in Polish.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised. Method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems identified.
Selective reporting (reporting bias)	Low risk	No problems identified.
Size	High risk	40 participants in cross-over.

Luben 1994

Methods	Randomised, double-blind, parallel group. Duration: 4 weeks.
Participants	71 participants with cancer pain from various sites; 48 with metastases. Mean age 63 years. Sex not reported.
Interventions	Tramadol 50 mg 4 times daily, n = 36.

Luben 1994 *(Continued)*

	Flupirtine 100 mg 4 times daily, n = 35. Dose could be increased to up to 6 times daily if needed.
Outcomes	PR: 5-point VRS. Participants with ≥ 1/5 and ≥ 2/5 point change in PI. Use of rescue medication. Clinician global impression of change. Adverse events. Withdrawals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised. Method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind with identical capsules.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems identified.
Selective reporting (reporting bias)	Low risk	No problems identified.
Size	High risk	36 in tramadol group, 35 in flupirtine group.

Mercadante 2005

Methods	Randomised, double-blind, double-dummy, cross-over study. Duration: 2 treatment periods of 3 days; no washout described.
Participants	60 participants with moderate to severe cancer pain (≥ 4/10, baseline PI 7/10), unresponsive to non-opioid drugs, non-neuropathic in origin. Mean age 66 years. Male 40%.
Interventions	Oral tramadol 100 mg twice daily. Rectal tramadol 100 mg twice daily.

Mercadante 2005 *(Continued)*

	Up to 4 doses of tramadol 50 mg orally allowed as rescue medication per day.
Outcomes	PI: 0 to 10 NRS and 4-point VRS. PR: 0 to 10 NRS. Symptom severity: 4-point VRS. Quality of sleep. Participant satisfaction. Participant preference. Adverse events. Withdrawals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised. Method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy method described, but detail of blinding not described - judged low risk.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Imputation not mentioned - analyses for participants who completed ≥ 1 cycle (50) and cross-over (44).
Selective reporting (reporting bias)	High risk	Outcomes were reported without supporting data.
Size	High risk	60 randomised in cross-over, but < 50 completed and provided data.

Rodriguez 2007

Methods	Multicentre, randomised, double-blind, parallel group. Duration: 3 weeks.
Participants	177 participants with moderate or severe cancer pain (baseline PI 7/10). Mean age 60 years. Male 50%.
Interventions	Tramadol 200 mg daily, n = 56.

Rodriguez 2007 *(Continued)*

	Paracetamol 2500 mg + codeine 150 mg daily, n = 59. Paracetamol 2500 + hydrocodone 25 mg daily, n = 62. Antidepressants or anticonvulsants for neuropathic pain allowed unchanged.
Outcomes	PI: 100-mm VAS. Participants with "at least some" PR. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned according to a computer generated schedule."
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Drug distribution was blinded with the drugs packaged in identical containers" with "appropriate number of tablets", but no indication of whether tablets were distinguishable.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems identified.
Selective reporting (reporting bias)	Low risk	No problems identified.
Size	Unclear risk	56 to 62 participants per group.

Wilder-Smith 1994

Methods	Randomised, double-blind, cross-over study. Duration: 2 treatment periods of 4 days, no washout period.
Participants	20 participants with 'strong pain' due to cancer (metastatic). Mean age 55 years.
Interventions	Tramadol solution 5%. Initial dose 50 mg 6 times daily. Morphine 1% solution. Initial dose 16 mg 6 times daily. Same dose used for rescue medication, then added to daily dose the following day.
Outcomes	PI: 5-point VRS.

Wilder-Smith 1994 *(Continued)*

	Participant symptom control (preference). Adverse events. Withdrawals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised. Method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The two solutions were adapted, to taste, smell and look identically and were then filled into coded drop dispensers with standardised pipettes by the hospital pharmacy."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The two solutions were adapted, to taste, smell and look identically and were then filled into coded drop dispensers with standardised pipettes by the hospital pharmacy."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems identified. Worst observation carried forward for early discontinuation.
Selective reporting (reporting bias)	Low risk	No problems identified.
Size	High risk	20 participants in cross-over.

Xu 2006

Methods	Multicentre, randomised, double-blind, cross-over study. Duration: single doses in sequence but timings not clear.
Participants	119 participants with moderate to severe cancer pain (> 4/10, baseline PI 61/100). Mean age 52 years (range 24 to 77). Male 43%.
Interventions	Arm A: dose 1 = CKLQ + placebo tramadol; dose 2 = placebo CKLQ + placebo tramadol; dose 3 = placebo CKLQ + tramadol 100 mg. Arm B: dose 1 = tramadol 100 mg + placebo CKLQ; dose 2 = placebo CKLQ + placebo tramadol; dose 3 = CKLQ + placebo tramadol. CKLQ is a combination of cobrotoxin 0.16 mg + tramadol 50 mg + ibuprofen 100 mg per tablet; 2 tablets per dose.
Outcomes	PI: 100-mm VAS every 10 minutes for 60 minutes. PI: 4-point VRS.

Xu 2006 *(Continued)*

	Participants with complete relief (PI = 0/100). Participants with partial relief (PI decreased to mild pain, score ≤ 4/10). Participants with no change (PI unchanged or > 4/10). Adverse events. Withdrawals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation. "Assignment written on a card and put into a sealed envelope."
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy design. "The placebo was formulated to be identical in color, taste, texture and package". All doses were 2 tablets of each intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy design. "The placebo was formulated to be identical in color, taste, texture and package". All doses were 2 tablets of each intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems identified.
Selective reporting (reporting bias)	Low risk	No problems identified.
Size	Unclear risk	Group sizes 59 and 60 participants.

CR: controlled release; EORTC: European Organisation for Research and Treatment of Cancer; n: number of participants per treatment arm; NRS: numerical rating scale; NSAID: nonsteroidal anti-inflammatory drug; PI: pain intensity; PR: pain relief; QoL: quality of life; VAS: visual analogue scale; VRS: verbal rating scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arbaiza 2007	Neuropathic pain in people with cancer.
Marinangeli 2007	Tramadol added to fentanyl.
Tassinari 2011	Systematic review.
Yavuz 2004	Tramadol for postoperative pain in gynaecological cancer pain.

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Pain/ (328885)
2. pain.tw. (411189)
3. 1 or 2 (552420)
4. exp Neoplasms/ (2827457)
5. (cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*).tw. (2670775)
6. 4 or 5 (3344191)
7. 3 and 6 (84189)
8. Tramadol/ (2467)
9. tramadol.mp. (3383)
10. k-315.mp. (10)
11. 8 or 9 or 10 (3393)
12. Acetaminophen/ (15188)
13. (acetaminophen or paracetamol or Panadol or Tylenol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (20846)
14. 12 or 13 (20846)
15. 11 and 14 (519)
16. 7 and 11 (248)
17. 7 and 15 (50)
18. 16 or 17 (248)
19. randomized controlled trial.pt. (414789)
20. controlled clinical trial.pt. (90619)
21. randomized.ab. (311705)
22. placebo.ab. (158104)
23. drug therapy.fs. (1852228)
24. randomly.ab. (220170)
25. trial.ab. (322366)
26. groups.ab. (1389663)
27. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (3518483)
28. exp animals/ not humans.sh. (4236009)
29. 27 not 28 (2997289)
30. 18 and 29 (202)

Appendix 2. CENTRAL search strategy

#1 MESH DESCRIPTOR Pain EXPLODE ALL TREES 32311

#2 pain:TI,AB,KY 83891

#3 #1 OR #2 88757

#4 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES 46196

#5 ((cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*)):TI,AB,KY 109552

#6 #4 AND #5 44635

#7 #3 AND #6 3519

#8 MESH DESCRIPTOR Tramadol EXPLODE ALL TREES 741

#9 tramadol:TI,AB,KY 2128

#10 k-315:TI,AB,KY 1

#11 #8 OR #9 OR #10 2129

#12 MESH DESCRIPTOR Acetaminophen EXPLODE ALL TREES 1873

#13 ((acetaminophen or paracetamol or Panadol or Tylenol)):TI,AB,KY 5644

#14 #12 OR #13 5644

#15 #11 AND #14 451

#16 #7 AND #11 53

#17 #7 AND #15 11

#18 #16 OR #17 53

Appendix 3. Embase search strategy

1 exp Pain/ (1002612)

2 pain.tw. (678037)

3 1 or 2 (1206185)

4 exp Neoplasm/ (3737489)

5 (cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*).tw. (3818206)

6 4 or 5 (4616390)

7 3 and 6 (246270)

8 Tramadol/ (15612)

9 tramadol.mp. (16228)

10 k-315.mp. (15)

11 8 or 9 or 10 (16240)

12 Paracetamol/ (73077)

13 (acetaminophen or paracetamol or Panadol or Tylenol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (77856)

14 12 or 13 (77856)

15 11 and 14 (5629)

16 7 and 11 (2044)

17 7 and 15 (896)

18 16 or 17 (2044)

19 random$.tw. (1115183)

20 factorial$.tw. (28388)

21 crossover$.tw. (58689)

22 cross over$.tw. (26130)

23 cross-over$.tw. (26130)

24 placebo$.tw. (243094)

25 (doubl$ adj blind$).tw. (171477)

26 (singl$ adj blind$).tw. (18123)

27 assign$.tw. (294263)

28 allocat$.tw. (107047)

29 volunteer$.tw. (210635)

30 Crossover Procedure/ (48290)

31 double-blind procedure.tw. (235)

32 Randomized Controlled Trial/ (416205)

33 Single Blind Procedure/ (22773)

34 or/19-33 (1740101)

35 (animal/ or nonhuman/) not human/ (5092256)

36 34 not 35 (1546286)

37 18 and 36 (334)

Appendix 4. LILACS search strategy

pain [Words] and (cancer$ or neoplas$ or tumo$ or carcinoma$ or hodgkin$ or nonhodgkin$ or adenocarcinoma$ or leukemia$ or leukaemia$ or metasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$ or myeloma$ or oncolog$) [Words] and tramadol or k-315 [Words]

Appendix 5. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Chapter 12, Higgins 2011).

- **High**: randomised trials; or double-upgraded observational studies.
- **Moderate**: downgraded randomised trials; or upgraded observational studies.
- **Low**: double-downgraded randomised trials; or observational studies.
- **Very low**: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports.

Factors that may decrease the quality level of a body of evidence are:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;
- indirectness of evidence (indirect population, intervention, control, outcomes);
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide confidence intervals);
- high probability of publication bias.

Factors that may increase the quality level of a body of evidence are:

- large magnitude of effect;
- all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect;
- dose-response gradient.

WHAT'S NEW

Date	Event	Description
18 February 2020	Amended	Clarification added to Declarations of interest.
6 November 2018	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 1, 2017
Review first published: Issue 5, 2017

Date	Event	Description
28 May 2019	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Draft the protocol	PW
Develop and run the search strategy	PW, SD PaPaS Information Specialist provided support
Obtain copies of studies	PW
Select which studies to include (2 people)	PW, SD
Extract data from studies (2 people)	PW, SD
Enter data into RevMan	PW, SD
Carry out the analysis	PW, SD
Interpret the analysis	All
Draft the final review	PW, RAM
Update the review	PW

DECLARATIONS OF INTEREST

PW: none known.

SD: none known.

RAM has received grant support from Grünenthal relating to individual patient level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attending boards with Menarini concerning methods of analgesic trial design (2014), with Novartis (2014) about the design of network meta-analyses, and RB on understanding pharmacokinetics of drug uptake (2015). He has received honoraria from Omega Pharma (2016) and Futura Pharma (2016) for providing advice on trial and data analysis methods.

This review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. As with all reviews, new and updated, at update this review will be revised according to 2020 policy update.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

  General institutional support

External sources

- The National Institute for Health Research (NIHR), UK.

  NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are several differences between the protocol and the review.

We amended secondary outcomes as a response to what was actually reported: 'Serious adverse events, defined as leading to withdrawal from treatment, including death' and 'Attrition: withdrawals due to lack of efficacy or adverse events.'

We updated GRADE wording to conform to more recent standards.

We amended outcomes to conform to more recent reviews in this series. The protocol planned to include: number of participants with pain reduction of 30% or greater from baseline, number of participants with pain reduction of 50% or greater from baseline, and adverse events in the 'Summary of findings' table. This has become 'number of participants with pain reduction of 30% or 50% or greater, participants with pain no worse than mild, and PGIC of much improved or very much improved'. We have also included serious adverse events, other adverse events, and withdrawals due to lack of efficacy or adverse events.

We made minor changes to the search strategy. We added a search of LILACS. The protocol incorrectly stated that we planned to contact experts in the field for unpublished and ongoing trials. This was not part of the plan, and was not done.

We added 'duration of study' to the planned subgroups.

We added Selective reporting (reporting bias) to the 'Risk of bias' assessment.

NOTES

A restricted search in November 2018 did not identify any potentially relevant studies. Therefore, this review has now been stabilised for three years following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [adverse effects] [*therapeutic use]; Analgesics, Non-Narcotic [adverse effects] [*therapeutic use]; Analgesics, Opioid [adverse effects] [*therapeutic use]; Cancer Pain [*drug therapy]; Drug Therapy, Combination; Randomized Controlled Trials as Topic; Tramadol [adverse effects] [*therapeutic use]

MeSH check words

Adult; Aged; Humans; Middle Aged; Young Adult